Mathematical Modelling, Vol. 7, pp. 1587–1600, 1986
Printed in the U.S.A.

0270-0255/86 $3.00 + .00

A GENERAL MODEL FOR THE SIMULATION OF BALANCE, IMBALANCE AND CONTROL BY AGONISTIC ANTAGONISTIC BIOLOGICAL COUPLES

E. BERNARD-WEIL

CNEMATER
Clinique Neurochirurgicale de l'Hôpital de la Pitié
83, Bd. de l'Hôpital
75013 Paris, France

(*Received* 4 *February* 1985; *revised* 12 *February* 1986)

A model of balance and imbalance for a couple of biological components has been first built in the field of the adrenal-postpituitary system. It can be also considered as a general model able to concern other types of balance and imbalance in various biological systems. Including at the same time state and control equations, it may be easily programmed on microcomputer. It can help to govern some more effective therapies, by suggesting "paradoxical" measures that the "common sense" does not sometimes enjoin to do it. We try to show how the microcomputer use and the clinical or biological insight are not contradictory, but one becomes stronger in connection with the other.

Although a concrete system (adrenal-postpituitary system) gave rise to the building of this model, it appeared as a model able to represent the behaviour of other systems, either in the biological field or in the field of man sciences.

The justification of this model called "model for the regulation of agonistic antagonistic couples" (MRAAC) was done in the original field where it was conceived[1–4]: simulation of the balance between vasopressin (VP) and adrenocortical hormones (ACH) defining the health state, simulations of the imbalance observed in various diseases, and of some optimal control procedures helping the physician to apply new types of therapies (particularly paradoxical therapies using the hormone already in excess in the patient's body).

We would like to see this model used in other fields, where the searchers could benefit of our mathematical and microcomputer experience with this model.

1. DESCRIPTION OF THE MODEL

1.1. *Characteristics of a general model (or model of function)*

It does not seem possible to precise the whole of the characteristics defining a general model, because such models are not crowds of them in the bio-mathematical practice at the present time. One is aware of the fact that the so-called knowledge models (KM) were in general preferred, seeing that they created an impression of being more closed to the observed facts. Nevertheless, other types of models would perhaps correspond to a better approach of the reality in some cases, especially as far as the control problems are concerned. So it would be perhaps possible to avoid the so-called counter-intuitive or perverse effects of some therapeutical trials.

The concept of function model seems to be fairly closed to some ideas of Rosen[5], showing that "functions" could act as subunits of a model instead of the usual "struc-

tures", basing upon the fact that models with different structures could perform the same function. In our opinion, a general or function model implies: (1) the lack of parameters with physical meaning, substituted with phenomenological parameters; (2) the existence of numerous hidden variables; (3) the use of particular constraints (cf. [5]), if it is necessary, to pass from a concrete system to another concrete system having the same function; (4) an use of the model that does not elicit only qualitative simulation (dynamical metaphor[5]) but ought to end also in experimentally confirmed quantitative results.

Here, the studied function was the balance function, concerning at the onset a neuro-endocrine couple. One can suppose that the fundamental mechanisms of balance, imbalance and control would be the same in other biological systems including a couple (or several couples)† of components acting upon a receptor.

Finally, building general models or models of function needs an empirical approach of the systems, prior to the formalization, very different from the usual one. Even if we perfectly know the whole of the data concerning the analytical knowledge of a system, we ought to be able to guess the basic paths or the general dynamical tendancies of the model functioning (for instance, in our own case, we did not seek to directly integrate in the formulas the whole of the data concerning the endocrine system, but only the general senses of the endocrine changes according to the states of health or diseases and to different ways of therapy: above all, a phenomenon had to be taken into account, i.e. the gap between the effects of cortisone *in vitro* (analytical knowledge) and the effects of cortisone *in vivo* (holistic or systemic knowledge), as far as the antimitogenic effects were concerned; the occurrence of a positive feed back upon the agonistic antagonistic hormone, the vasopressin, was postulated then detected in order to explain such a discrepancy (cf. Appendix 1). Therefore, the known actions of both components have to be regrouped under the headings of agonism (actions of the same sense) and of antagonism (actions of opposite senses), as it was done for the endocrine system in question.

1.2. *Specific properties of the model (agonism–antagonism, included optimal control)*

Most of the models concerning the actions of a two-elements process (cf. review infra) took into account only the actions of opposite type (for instance excitation–inhibition). But considering only the antagonistic actions seemed to us not enough for an effective use of a model belonging to such a category. It seemed to be necessary to distinguish two basic systems of regulation: the first one checked an imbalance between both elements (the difference if their values were expressed in positive units),‡ and the second one checked an imbalance in relation to the value of the set-point where the antagonistic balance (or imbalance) occured. So, relative and absolute values of both elements were separately considered then combined in the definitive model. The terms used to define both types of regulation were "antagonistic" and "agonistic": the meanings of these terms are a bit different from the use of such terms in pharmacological studies, where an agonist can be anything which activates an activator or inhibits an inhibitor . . . , but they correspond to the two types of action recognized inside the couple, to roughly speaking, the adversive and the synergic effects—the more so as that the term of antagonism was already used, as we do it, in the models quoted infra. As other advantages of such a view, one can observe that the antagonistic aspect may rather correspond to the behavior of the system considered as closed (for instance, under the form of a limit cycle), and the ag-

† In this paper, only the mathematical model concerning one couple is described, but the problem of interacting couples on the same receptor has been studied too.

‡ Theoretically, the balance may correspond to a fixed value of the difference, but such a possibility will not be formalized in this paper.

onistic aspect rather correspond to the behavior of the system considered as opened (agonistic inputs cause limit cycle to "climbing" or "going down" as a whole).

Besides these points, this model differed also from the other models concerning interaction of pairs of antagonistic processes, by the inclusion of an optimal control tool in the model, as soon as the model building was begun.

1.3. *Basic form of the model*

It was constituted by four nonlinear differential equations, based on a kind of "series expansion" of antagonistic and agonistic expressions.

$$\begin{aligned}
\dot{x} &= k_1(u + r) + k_2(u + r)^2 + k_3(u + r)^3 + c_1(v + s) \\
&\quad + c_2(v + s)^2 + c_3(v + s)^3, \\
\dot{y} &= k_1'(u + r) + k_2'(u + r)^2 + k_3'(u + r)^3 + c_1'(v + s) \qquad (1) \\
&\quad + c_2'(v + s)^2 + c_3'(v + s)^3, \\
\dot{X} &= k_5(u + r) + k_6(u + r)^2 + k_7(u + r)^3 + c_5(v + s) \\
&\quad + c_6(v + s)^2 + c_7(v + s)^3, \\
\dot{Y} &= k_5'(u + r) + k_6'(u + r)^2 + k_7'(u + r)^3 + c_5'(v + s) \qquad (2) \\
&\quad + c_6'(v + s)^2 + c_7'(v + s)^3,
\end{aligned}$$

$u(t) = x(t) - y(t)$; $r(t) = X(t) - Y(t)$; $v(t) = x(t) + y(t) - m$; $s(t) = X(t) + Y(t)$; x = endogenous ACH for instance; y = endogenous VP for instance; X = exogenous ACH for instance; Y = exogenous VP for instance; k_i, c_i, m = constant parameters; (1) = state equations; (2) = control equations; other inputs were added for various experimental conditions: $p(t)$, antagonistic stimulus in the expression $u(t)$, for instance as an osmotic stimulus and $q(t)$, agonistic stimulus in the expression $v(t)$, for instance as a volemic stimulus or a stress.

This model ended to re-establish the balance in case of imbalance, i.e. if $x \neq y$, $x + y \neq m$.

First, let us consider the state equations (1) alone, without r and s (i.e. without control variables). If the singular point $(x, y) = (m/2, m/2)$ is stable, either as a stable focus or under the form of a limit cycle, then x and y will return to these values after a perturbation (in the absence of other attractors).

If the singular point $(x, y) = (m/2, m/2)$ is not stable, then the trajectories of $x(t)$, $y(t)$ will end upon another singular point, so-called pathological, according to the phase-plane representation of the model for a given parametrical field.

Secondly, let us consider together the state and the control equations (1 and 2), after that a lasting imbalance has occurred. By choosing a convenient parametric field for the control equations,† it becomes possible to re-establish a global balance defined by $(x + X, y + Y) = (m/2, m/2)$.

1.4. *Constraints*

In principle, the constraints are dependent on the precise type of the concrete system that has to be modeled. As an example, the constraints used in the modeling of the endocrine system are indicated.

† One suppose that the biologist or the physician cannot directly modify the parametric field of the state equations.

1.4.1. *Constraints of positivity for* x *and* y. To reach this end, m became variable in relation to time, by rising when x and y approached a minimum (due to the effects of various inputs, hypervolemia for instance, or hormonal input). $m(t)$ return to the initial value when the inputs ceased by means of a second-order differential equations acting as a spring.

1.4.2. *Synchronizer.* This device avoided the appearance of a phase shifting of the limit-cycle corresponding to the circadian rhythms of x and y (cortisol and vasopressin), due for instance to stimuli $p(t)$. Such a phase shifting did not happen in the biological system (the acrophase remained at the same time of the day). Instead of v, we had:

$$\bar{v} = v + A \sin(\omega t + B) + q(t) \qquad A, B = \text{constant parameters.} \tag{3}$$

$\bar{v}$ was also used to stimulate the effects of oversea flights on the circadian rhythms.

1.4.3. *Other expressions for* u *and* v. v was usually substituted with nonpolynomial expressions in order to take into account the log-dose response of the cell to hormones:

$$\bar{v} = m \log((x + y)/m) + q(t) + \text{synchronizer.} \tag{4}$$

An allosteric expression has been also proposed for u.

1.4.4. *Variable parameters.* In order to explain the mechanism of transition between a physiological and a pathological field, we admitted that some inputs could act upon the parameter values k_i, c_i. For instance:

$$\ddot{k}_i + \alpha\dot{k}_i + \beta(k_i - f(q(t)) - k_{io}) = 0 \qquad \alpha, \beta = \text{constant parameters,} \tag{5}$$

k_{io} = reference value of the parameter,

$f(q(t))$ = effects of stress that could be aleatory provoked,

was added a device to forbid the parameter to return to its initial value, when the change exceeded a given increment.

2. HINTS TO A GOOD USE OF THIS MODEL, ESPECIALLY FOR MICROCOMPUTER SIMULATION

2.1. *Preformalization working*

It seems to be convenient to find out two components in the considered concrete system that may be considered as the major components of the system and that act in an agonistic antagonistic manner. Moreover, these components have to exist outside the body, allowing their therapeutical use (let us recall that x, y were in our example the secreted hormones and X, Y the injected similar hormones). The fashion of considering the concrete system ought also to be reorganized. It has to centre on the agonistic antagonistic aspects of the biological functioning (cf. supra). Finally, some common units have to be chosen (for instance, 1 common unit = the mean concentration of each hormone at the state of equilibrium).

2.2. *Mathematical study*

As it was usually the case for the nonlinear models, a qualitative approach of the equation behavior may be made. It represents a first step before the computer simulation.

2.2.1. *Stability conditions of the state equations.* The goal is to obtain a stability of the so-called physiological point $(x, y) = (m/2, m/2)$. For most of the applyings, it seems convenient to obtain such a stability, as well in an asymptotically manner as under the form of a limit cycle. We advise to transform equations (1) and (2) in equations $\dot{u}$ and $\dot{v}$ for the stability study ($\dot{u} = \dot{x} - \dot{y}$, $\dot{v} = \dot{x} + \dot{y}$), a procedure that simplifies the condition discussion.

2.2.1.1. By linearization, one finds the following conditions for $(u, v) = (0, 0)$ to be stable:

$$\begin{aligned} &\text{(a) } \bar{k}_1 - \bar{k}'_1 + \bar{c}_1 + \bar{c}'_1 < 0 \qquad \text{if we want asymptotical stability,} \\ &\text{(b) } \bar{k}_1 - \bar{k}'_1 + \bar{c}_1 + \bar{c}'_1 > 0 \qquad \text{if we want a limit-cycle (cf. infra),} \\ &\text{(c) } (\bar{k}_1 - \bar{k}'_1)(\bar{c}_1 + \bar{c}'_1) - (\bar{k}_1 + \bar{k}'_1)(\bar{c}_1 - \bar{c}'_1) > 0. \end{aligned} \tag{6}$$

(6c) can be rewritten as $k_1 c'_1 - k'_1 c_1 > 0$.

2.2.1.2. By the second Lyapounov's method (by choosing Lyapounov's function $V = \frac{1}{2}(u^2 + v^2)$ with $\dot{V} = u.\dot{u} + v.\dot{v}$), one finds the following conditions for a global stability of the point $(u, v) = (0, 0)$:

$$\begin{aligned} &\bar{k}_1, \bar{k}_3, \bar{c}'_1, \bar{c}'_3 < 0, \qquad \bar{k}'_1 + \bar{c}_1 = 0, \\ &\bar{c}_3 = \bar{k}'_3 = \bar{k}_2 = \bar{c}_2 = \bar{k}'_2 = \bar{c}'_2 = 0. \end{aligned} \tag{7}$$

To notice that

$$\bar{k}_1 = k_1 - k'_1 \ldots \bar{k}'_1 = k_1 + k_1' \ldots$$

In particular, such a parametric field allows an instable focus (6b) to become a limit cycle. But the above conditions are too drastic, and other values for the "quadratic" parameters may be tolerated without the occurrence of a global instability.

2.2.1.3. By the method of studying the trajectories at the infinite (by letting $v = \mu u$ then calculating $\dot{v}/\dot{u}$ at t_∞), one obtains the following equation:

$$\bar{c}_3 \mu^4 - \bar{c}'_3 \mu^3 + \bar{k}_3 \mu - \bar{k}'_3 = 0. \tag{8}$$

The global stability corresponds to a lack of real roots for such an equation (μ is the slope of the asymptotical straight lines for the trajectories of u, v at the infinite). For instance (8) has no real roots with $\bar{c}_3\, \bar{k}'_3 < 0$ and $\bar{k}_3\, \bar{c}'_3 < 0$.

This third method allows us to hope to obtain a good global stability of the physiological point, even if the "quadratic" parameters have a value $\neq 0$.

To summarize the conditions for the "linear" and "cubic" parameters, they are satisfied, for instance, with:

$$\begin{aligned} &k_1, k'_1, c'_1 < 0, \qquad c_1 > 0, \\ &k_3, c'_3, c_3 < 0, \qquad k'_3 > 0, \qquad |k_3| > |k'_3| \qquad |c'_3| > |c_3|. \end{aligned} \tag{9}$$

but other choices would be convenient ($k_1, k'_1, c'_1 > 0 \qquad c_1 < 0 \ldots$).

2.2.1.4. With the aid of such conclusions, it is allowed to qualitatively simulate the model functioning in diverse circumstances and to establish phase-portraits corresponding to various types of behavior for a concrete system: physiological stable or instable at-

tractors, pathological stable or instable attractors, and various combinations between these attractors.

2.2.2. *Number and nature of the singular points.* To know the number of the singular points, eqns (1) must be solve with $\dot{x}$ and $\dot{y} = 0$ (or the transformed equations in $\dot{u}$, $\dot{v}$ with $\dot{u} = \dot{v} = 0$). It was not possible to do it analytically. For a given parameter field, the phase-plane plottered by the microcomputer answered this problem and precised the nature of the points: node, focus, limit cycle or saddle point. More speedily, drawing the nullclines showed the diverse singular points corresponding to the intersects of the nullcline loci (by using a program "polynominal rootfinder" for microcomputer).

2.3. *Elasticity study*

Such a study helped us to better understand the role played by each group of parameters. We have to solve the system[6]

$$\begin{aligned} \dot{\mathbf{S}}_{i,j}(t) &= \mathbf{G}(\mathbf{S}_{ij}(t), \mathbf{X}(t), \mathbf{P}_{ij}) \qquad i = 1, 2 \qquad j = 1 \text{ to } 6 \\ \dot{\mathbf{X}} &= \mathbf{F}(X) \\ \mathbf{G} &= \frac{\partial \mathbf{F}}{\partial \mathbf{X}} \cdot S + \frac{\partial \mathbf{F}_i}{\partial \mathbf{P}_{ij}}, \end{aligned} \tag{10}$$

S = sensibility coefficients; X corresponds to x, y of (1); $\partial F/\partial X$ = Jacobian matrix.

Finally, elasticity coefficients were given by

$$E = \mathbf{S}_{ij} P_j / X_i. \tag{11}$$

Table 1 points out the results for a physiological parametric field. The extreme values of the elasticity coefficients are kept away for the "linear" parameters and nearer for the

Table 1. Elasticity coefficients. Here are reported the minimum and maximum values of $E(t)$ (cf. 2.3) for every parameter and variable. The amplitude of the changes are higher in the case of the "linear" parameters k_1, c_1, k_1', c_1', the "quadratic" parameters k_2, c_2 and the "cubic" parameters k_3', c_3', in order of importance.

	$x(t)$		$y(t)$	
	min	max	min	max
k_1	−55.6	28.0	−35.7	.2
c_1	−129.5	242.9	−.1	176.5
k_2	−23.9	47.1	−.1	31.5
c_2	−96.1	50.4	−68.1	.1
k_3	−5.3	2.9	−3.8	.1
c_3	−4.6	2.5	−3.3	.1
k_1'	−7.1	12.6	−4.2	10.0
c_1'	−67.3	36.8	−51.8	.8
k_2'	−3.1	1.7	−2.4	1.6
c_2'	−2.2	4.0	−.1	3.2
k_3'	−7.8	13.9	−3.0	10.8
c_3'	−5.3	2.9	−4.0	.1

"quadratic" parameters, while they are more closer yet for the "cubic" parameters. Nevertheless, the whole of the parameters is necessary to correctly simulate the system modeled by these equations. If the elasticity of the "cubic" parameters is weak, only these parameters authorize a satisfactory stability of the model.

2.4. *Microcomputer study*

It was already used to verify the inferences of the mathematical studies (sec. 2), but it has its own goals. All our working was done with a Hewlett Packard 9825B and an Apple II (with a 8088-card plus a Tasc compilator). Let us give some results that could save time for some eventual applyings of this model to other biomedical fields.

2.4.1. *Methods of integration.* Order 4 Runge–Kutta method seemed valid. A step length of .2 (for 24 hours = 48 steps) was generally used. Smaller lengths could be more satisfactory in some cases (for instance when the inputs were important and the logarithmic expression was used).

2.4.2. *Quantitative identification.* We had to minimize the objective function J:

$$J_{k_i,c_i} = \sum_i (\bar{x}_i - x_i)^2 + \sum_i (\bar{y}_i - y_i)^2 \qquad \begin{matrix} \bar{x}, \bar{y} = \text{experimental values,} \\ x, y = \text{values given by the model.} \end{matrix} \tag{12}$$

Two methods were resorted to: a method without using derivatives such as Hooke–Jeeves's method[7] and a method using derivatives and conjugate directions, the method of Davidon–Fletcher–Powell[8, 9]. The results were not very different, particularly as far as the parameter values found by both methods allowed us to observe a good stability of the model [cf. the phase portraits in Figs. 1(a) and 1(b)].

2.4.2.1. Choice of the initial parametric field. This choice was very important if we did not want to observe a blockade of the identification process far from the minimum of J. We advise to give: (1) zero values to the "quadratic" parameters; (2) to the "linear" parameters some values such as the natural frequency of the linearized system roughly corresponds to the period of the biological cycle (for instance, $k_1 = k_1' = c_1' = -.3$ and $c_1 = .3$ with 48 steps for 24 hours); (3) to "cubic" parameters some values derived from the stability theory study (Sec. 2) (for instance $k_3 = -1$ $k_3' = 1$, $c_3 = -1$, $c_3' = -1$). Ponderation of the residuals was also useful (by multiplying the residuals by the inverse

Fig. 1. Phase plane representations of two parameter identification results. (a) with the Davidon's method; (b) with the Hooke–Jeeves's method. Results were similar as far as the global stability was concerned. It seems that the identification process does not only consist in fitting a curve, but also asks for a stability of the whole of the trajectories, whatever are the initial conditions.

of the variance). As far as Hooke–Jeeves's method was concerned, the initial step size has to be not too high in order that the "linear" parameters could display some noticeable changes (for instance, $\Delta = .02$).

2.4.2.2. Experimental data. They could consist: (1) in the successive values of the circadian rhythms of the two chosen components; (2) and/or some data obtained after that some inputs have been added [for instance, the effects of an hemorrhagie upon the plasmatic concentrations of VP and ACH; in these cases, we had to add the input values (agonistic or antagonistic inputs, hormonal input) in eqns (1) at the corresponding time]. Another problem was to find some common units, not only for both components, but also for the inputs other than the endocrine inputs.

A first series of conclusions could be drawn from these comments: the suitable data were not always present in the literature and the use of this model, whatever the particular biological field studied, ought to lead to some new types of experimental and clinical investigations [for instance, the simultaneous dosages of vasopressin and ACH was (and is yet) rather seldom by the researches about adrenal-postpituitary physiology or pathology].

2.4.2.3. Results. Finally, these methods did not allow to us to find the absolute or global minimum of J. The J function was likely not convex. However, our experience showed that the results, although somewhat different from one method to another, and different with the same method according to the details of procedure (step size, initial conditions . . .), can be considered as very similar, noticeably as far as most of the parameter signs and relative values of the parameters were concerned (Fig. 2) (Appendix 2).

2.5. *The problem of the optimal control*

All the preceding comments were connected with the state equations. One should stress the fact that the MRAAC included control equations that were conceived in the same time as the state equations. Reduced to (1), this model could be criticized if compared with the KM (cf. discussion in 3.2.). Thus, control was also the task it had to fulfill.

2.5.1. *Choice of the control variables.* They ought to correspond to the same elements as x and y, i.e. X and Y (as it was the case when the model was applied to check the adrenal-postpituitary disturbances) (cf. Appendix 1). One may perhaps looking at a control action by the mean of $p(t)$ and/or $q(t)$.

2.5.2. *Objective function.* The problem was rather different from this encountered

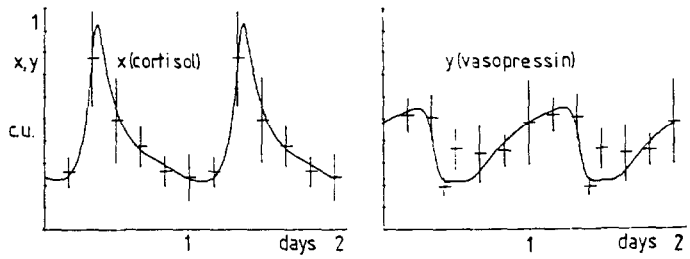

Fig. 2. Results of the parametric identification of eqns (1) from the experimental circadian rhythms values of cortisol and vasopressin, by means of the Hooke–Jeeve's method. The sum of the residuals was 7.8% of the sum of the experimental values (5.7% for cortisol values, 9.6% for vasopressin values).

with the usual methods of optimization. Theoretically, it was not the case of an objective function to minimize, but the problem asked to looking for the stability of the point:

$$(x + X, y + Y) = (m/2, m/2) \tag{13}$$

by hypothesizing that the receptors of the endocrine actions did not distinguish between x and X, y and Y.

This end could be easily reached if one contemplated only doing an asymptotical balance. The choice of the control parameters could be done after the transformation of the set of equations (1) and (2):

$$\begin{aligned} \dot{z} &= \dot{x} + \dot{X} = (k_1 + k_5)(z - w) \cdots + (c_1 + c_5)(z + w - m) \ldots \\ \dot{w} &= \dot{y} + \dot{Y} = (k_1' + k_5')(z - w) \cdots + (c_1' + c_5')(z + w - m) \ldots \end{aligned} \tag{14}$$

Then the conditions of stability for (14) were the same as those already seen if Sec. 2.2 (Fig. 3). To remark that "linear" parameters alone might allow us to fulfill such an optimal control task.

When we proposed to reestablish the physiological oscillatory balance (the circadian rhythms for instance), the problem seemed somewhat different. Theoretically, it would be enough to choose $k_5, k_6, k_7, c_5 \ldots k_5', k_6' \ldots$ such as $k_{1\,\text{patho}} + k_5 = k_{1\,\text{physio}}, \ldots$. In fact, if we acted in this way, we observed in general a stability of $(z, w) = (m/2, m/2)$, but not a stability of x, y, X, Y, separately considered: a "drift" of the order 4 limit cycle (x, y, X, Y) appeared.

In these conditions, it was proposed to add some kinds of "penalties" to the control equations (2):

$$\begin{aligned} \dot{X} &= \cdots + \lambda_1(X - \bar{X}) + \lambda_2(X - \bar{X})^2 + \lambda_3(X - \bar{X})^3, \\ \dot{Y} &= \cdots + \lambda_1'(Y - \bar{Y}) + \lambda_2'(Y - \bar{Y})^2 + \lambda_3'(Y - \bar{Y})^3, \end{aligned} \tag{15}$$

λ_i, λ_i' = constant parameters, $\bar{X}, \bar{Y}$ = constant parameters. Then, the objective func-

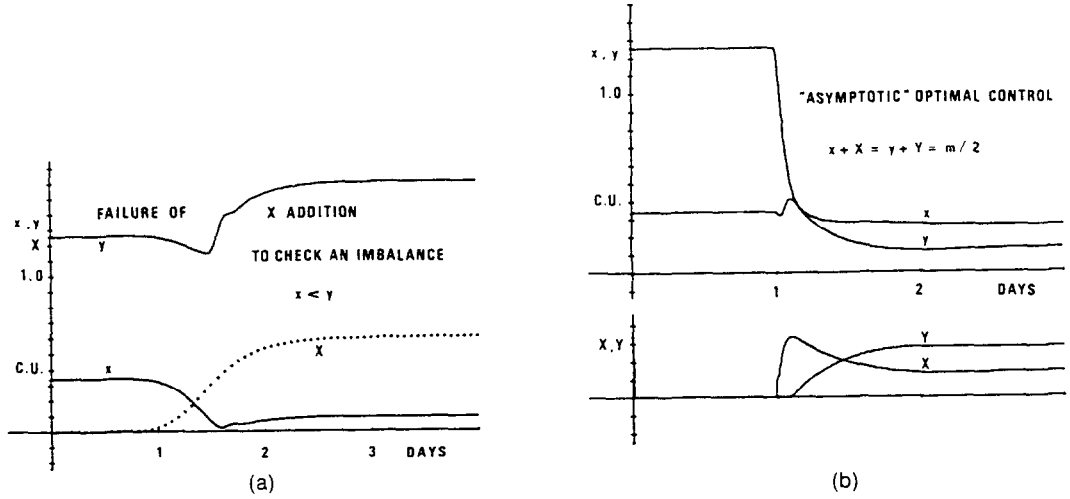

Fig. 3. Use of the optimal control [with eqns (1) and (2)]. (a) Noneffective action of the administration of X alone when an imbalance $x < y$ was elicited by a change in the parametric field: y remained higher than $x - X$. (b) Theoretical example of asymptotical optimal control [by using eqns (1) and (2)]: X and Y had to be added in order that the singular point $(x + X, y + Y)$ equalled $(m/2, m/2)$. C.U. = "common" units.

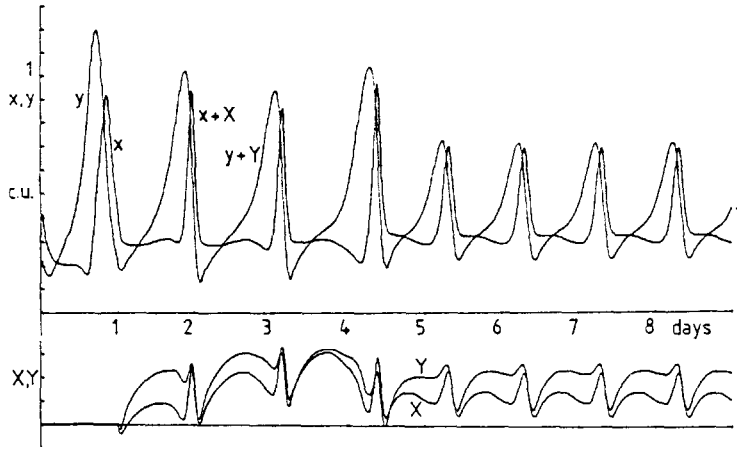

Fig. 4. Cyclic optimal control: from a cyclic (and no longer asymptotic) imbalance, it was possible to reestablish the circadian rhythms pattern of x and y by means of a cyclic addition of X and Y (cf. text).

tion $\hat{J}$ had to be minimized:

$$\hat{J}_{k_i,c_i,\lambda_i} = \sum_i (\bar{x}_i - x_i - X_i)^2 + \sum_i (\bar{y}_i - y_i - Y_i)^2.$$

Such procedures demanded a rather long time with a microcomputer, the more so as such optimization had to be done over several 24 hour cycles (6 to 8, the objective function concerning only the three or two last cycles, with the adjonction of diverse constraints: of positivity for x, y, X, Y and a constraint of periodicity [minimize: $(X_{\text{final time}} - X_{\text{final time}} - T)^2$, T being the period time)]. Yet it was possible, after 2 or 3. n iterations (n = number of the parameters) in the case of the Davidon's method, to have an idea of the proposed control (Fig. 4 after 5 .n iterations).

3. CONCLUSIONS ABOUT THE MEANING OF THE MRAAC

3.1. *MRAAC and biomedicine*

3.1.1. *Difficulties to admit a model of function.* The physician and the biologist are generally not accustomed to the use of such models. They can believe that a model must closely reflect the reality and they could express the following remarks: (1) x and y, in the endocrine model, corresponded to some actions rather than to some plasmatic concentrations: it was the reason for what the use of nonpolynomial agonistic and antagonistic expressions was considered—seeing that it was not easy to find out some types of variables marking such actions (cyclic AMP for VP ?; ARN messenger for ACH or measure of the complexes hormone-receptors ?) or the sum of these actions (volemia ?) or their difference (water diuresis?), unless one accepts as an approximation a roughly parallelism between hormonal action and hormonal concentration; (2) the identification of the parameters included in some devices as the synchronizer or the constraints of positivity, elicited some problems too; (3) finally, biologists and physicians could be astonished to the notion itself of phenomenological parameters and to the very simplified form of the equations in relation to the known complexity of the concrete systems.

3.1.2. *Responses to these objections.* First, the notion of knowledge models is itself

questionable: what is sometimes the reality of the compartments and of the rate constants in compartmental analysis? On the other hand, a KM, taking into account the whole of the knowledge about a concrete system, could perfectly simulate one phenomenon (a curve of data) belonging to the biological system, but had to be changed sometimes to be able to fit another phenomenon (another curve of data) belonging to the same system. Such facts did not seem due to the mathematical working itself, but mainly to the defective experimental knowledge of a given concrete system (especially as far as cell events were concerned, even if there were some interesting models about the hormonal effects on the cell receptors and metabolic changes beyond the receptors).

On the contrary, the models of function try to fill such gaps, by satisfying themselves to reflect only the general outline of the systems.

Moreover, there is a long literature on biological behavior as the outcome of pairs of antagonistic processes, which could sometimes may have a concern in such an epistemological frame. A first current was illustrated by the papers of Hill[10] and Turing[11], Rashewski[12], Rosen[13], who proposed some linear model with two-factor elements, corresponding to excitation and inhibition processes, combined with an observable related to these variables in a nonlinear way. These models concerned often nervous excitation, but one of these authors was "aware of fruitful analogies between such apparently dissimilar biological phenomena as cellular control in epigenesis and learning"[13]. Another current was rather based on nolinear models exhibiting limit-cycles that could be the result of interactions between excitation and inhibition, such as the models of Bonhoeffer–van der Pol (in [14]), Hess and Boiteux[15], Goldbeter and Nicolis[16]. Let us quote too the models of Goodwin[17], Thom[18], Monod–Wyman–Changeux[19], Yagil[20], Rubinow and Segel[21], Meinhardt[22]—this last one with partial differential equations—which were looking for modeling enzymatic reactions or morphogenesis from a near point of view. Finally, Thom's model[18], by the way of two basin attractors (in the case of the double cusp), also represented another type of antagonistic dynamical metaphor.

Nevertheless, it is unlikely that the quoted models could be very useful for solving the problems elicited in the present paper: quantitative simulation and control of (im)balanced oscillating couples, noticeably for the reasons exposed in 1.2 and 1.1. They seem to be either too much general or too much related to a specific field, although these models have likely fine prospects before them in the bio-mathematical research.

3.1.3. *Chief justification of the MRAAC.* After all, it only means a component of an agonistic antagonistic couple to vary at a given time $(\dot{x}, \dot{y})$ in relation to the state of agonistic antagonistic balance (or imbalance) for the considered system (u, v). Such an assertion, of logical type, could be admitted by everybody.

3.1.4. *Domain of biological applyings.* It seems to spread from the microscopical cybernetics (activator–inhibitor dialectics) up to "higher" biological or even psychological systems, where balance and growth could be simulated by this model. Rather than the usual concept of hierarchical levels in the body, we would emphasize the fact that the same model perhaps intervenes at anyone of these levels.

The main goal of this model, or similar models, could be to aid to the physician in order to fight the adverse or counter-intuitive or perverse effects of a drug (primarily or secondarily) when the agent impeding the effects of this drug might be recognized.

3.1.5. *Pedagogical use of the MRAAC with a microcomputer.* In our experience, the students appreciated the opportunity to look at the computer screen where appeared the reults of the equation set integration: simulation of the self-checking of the normal balance, simulation of the types of endocrine imbalance encountered in the patients of a neuro-

surgical department, simulation of the noneffective or not enough effective action of the corticoids alone, demonstration of the need to resort to a "paradoxical" therapy including both hormones.

As the same one can say: "The more the quality of the clinical or biological insight, the more the accuracy of the corresponding formal model", one can reverse the terms: "the building of a good formal model aims to develop (and not to reduce) the insight capacities".

3.2. *MRAAC and epistemology*

Such problems have been already met in the preceding paragraphs. Some remarks may be added.

3.2.1. *General systemic approach.* Considering both opposite aspects of a phenomenon was an end already asserted by diverse authors[23–25]. The double-bind of Bateson[26] belonged also to this field of researches (it is worth noting that this type of empirical and not formal modeling gave rise to some paradoxical therapies in the psychiatric domain, by means of strengthening the pathological symptom). Delattre[27] formally studied the problem of the inverse regulations, analogous to the perverse or counter-intuitive effects of a bad control, especially when a pair of opposite actions was concerned. Truly speaking, such ideas are not yet very propagated in the physician's mind: microcomputers could facilitate their diffusion that might be made easier with personal handling of these tools and curve simulations.

3.2.2. *Precursors of the agonistic antagonistic modeling.* This problem seems to go beyond the frame of a biomathematical paper, but it seems important to know that some dynamical binary structures exhibiting an agonistic antagonistic behavior were encountered by various philosophers or even theologians. Although such an inquiry may seem to be unusual and questionable, one can study how the interactions of two opposite and cooperative concepts were considered by Hegel, Saint-Bonaventure, the Zohar book, the Presocratics and the Bible, and what were the answers given to this problem—more or less closed to the biomathematical current reported in the present paper. In the same way, from Wittgenstein and Freud to Heidegger and Winnicott, a more recent research was undertaken, which was seeking after the role played by oppositional couples in mind and knowledge processes, and which could help to go beyond the limits imposed by the reductionnistic point of view to the modeling activity[28, 29].

APPENDIX 1

Results obtained with the MRAAC in the adrenal postpituitary field[1–4]

A.1. *Agonistic and antagonistic actions of VP and ACH.* It was possible, as far antagonisme was concerned, to oppose ACH (ACH = cortisol + aldosterone considered as a whole) to VP: ACH had an effects of sodium retention with a potassium deprivation by the kidney and a water diuretic effect eliciting a water shift from the cell compartment to the extracellular one; instead VP, while it was not really possible to oppose both categories of hormones in every particular, provoked cell overhydration with water antidiuresis and a decrease of the plasma sodium concentration. In the second group of agonistic actions, ACH and VP acted in the same manner, seeing that both favoured volemic expansion. The regulatory stimuli themselves may be put under the heads of antagonism (osmotic stimuli) and of agonism stimuli (volemic stimuli or stress).

A.2. *Simulations with this model.* It gave rise to various simulations of the system behavior (at a macroscopical level in a way) in various conditions: first, quantitative identification of the parameters for the coupled circadian rhythms by normal subjects (as reported above), then, from these parameter values, simulations on the whole of the adrenalectomy effects, neuro-posthypophysectomy effects, of hypervolemia, hypovolemia, hyperosmolarity, hypoposmolarity effects, simulations of stress, simulations of the different effects of cortisol upon the endogenous secretion according to the time administration . . . (at least the senses of the observed changes in the concrete system were found again in the curves given by the microcomputer); then, simulations of the pathological phenomena by means of a change in the parametric field (noticeably VP > ACH imbalance), demonstration of the impossibility to check the imbalance with the alone administration of the insufficient hormone (ACH); suggestions brought out by the optimal control [eqns (1) + (2)] in favour of a simultaneous administration of VP and ACH for the therapy of such imbalances.

A.3. *Therapeutics inferences.* Therapeutics roughly corresponding to the results of the optimal control were used in the following fields: (1) hydration disorders by neurosurgical patients (cerebral edema or collapsus), and (2) palliative treatment of some cerebral tumours (recurrent grade II astrocytomas, cerebral metastases from breast cancer origin)[30].

To justify these last attempts, one may recall the existence of a not yet well-known mitogenic effect of VP[31–33] opposite to the ACH actions in the same circumstances (cell cultures); as well as the recognition of a special type of host-tumour interrelationships characterized by a VP/ACH imbalance by cancerous subjects, outside the frame of the Schwartz-Bartter's syndrome[34].

APPENDIX 2

Quantitative identification of the physiological parametric field

With the Hooke–Jeeves's method, $k_1 = -.0550$, $c_1 = .6650$, $k_2 = -.7425$, $c_2 = 2.640$, $k_3 = -3.165$, $c_3 = 2.475$, $k_1' = -.0775$, $c_1' = -.190$, $k_2' = .210$, $c_2' = -.4275$, $k_3' = .225$, $c_3' = -2.900$. With the Davidon's method, the values were $-.2008$, $.9488$, -1.006, 3.390, -2.5215, $.02125$, $-.0310$, $-.3599$, $.2273$, $-.8578$, $.2543$, -1.329 respectively. Equation (4) was used. In eqn (3), $A = .1$, $B = -.5235$ [maximum of $A \sin(\omega t + B)$ at 8 hours A.M.].

Experimental values were found in[35, 36]. 0.4 C.U. ("common" unit) equals 1.1 μg/ml of plasmatic VP or 77 ng/ml of plasmatic cortisol. $m = .8$. Other attempts to identification with $x(t)$ corresponding to a weighted combination of cortisol and aldosterone is under study.

REFERENCES

1. E. Bernard-Weil and J. Mulletin, A mathematical model for the study of adrenal-postpituitary interrelationships: its use in the correction of an antagonistic imbalance. *Math. Biosci.* **8**, 181–189 (1970).
2. E. Bernard-Weil, M. Duvelleroy, and Y. Cherruault, Computer analog simulation of a model for the regulation of agonistic antagonistic couples. *Biomed. Comput.* **9**, 191–213 (1978).
3. E. Bernard-Weil, Formalisation du système hormonal surréno-posthypophysaire par le modèle mathématique de la régulation des couples ago-antagonistes. Ph.D. Thesis, University Paris-VI (1979).
4. E. Bernard-Weil, Identification and control of the model for the regulation of agonistic antagonistic couples. Medical applications in the field of the neurosurgery and cancerology, in *IFIP Conference on Mathematical Modeling in Immunology and Medicine* (G.I. Marchuk and L. N. Belykh, ed.), pp. 267–275, North-Holland, Amsterdam (1983).
5. R. Rosen, Biology and systems research: an overview, in *Applied General Systems Research* (G. Klir, ed.), pp. 489–510, Plenum Press, New York (1978).

6. F. Santi, Identification du modèle de la régulation des couples ago-antagonistes. Applications au système surréno-posthypophysaire. Contrôle. IIIrd Cycle Thesis, University Paris-VI (1982).
7. R. Hooke and T. A. Jeeves, Direct search solution of numerical and statistical problems. *JACM* **8**, 212–229 (1961).
8. W. C. Davidon, Variable metric method for minimization. AEC Res. and Div. Report. ANL-5990 (revised).
9. R. Fletcher and M. J. D. Powell, A rapidly convergent descent method for minimization. *Computer J.* **6**, 163–168 (1963).
10. A. V. Hill, Membrane phenomena in living matter: equilibrium or steady state. *Trans. Faraday Soc.* **26**, 667 (1930).
11. A. Turing, The chemical basis of morphogenesis. *Philos. Trans. Roy. Soc. London B* **237**, 37–72 (1952).
12. N. Rashewski, *Mathematical Biophysics. Physico-Mathematical Foundations of Biology* Vol. 1, pp. 389–404, Dover, New York (1960).
13. R. Rosen, *Dynamical System Theory in Biology*, Vol. I, Wiley Intersciences, New York (1970).
14. R. Fitzhugh, *Mathematical Models of Excitation and Propagation in Nerve*, National Institute of Health, Bethesda (1968).
15. B. Hess and A. Boiteux, Oscillatory phenomena in biochemistry. *A Rev. Biochem.* **40**, 237–258 (1971).
16. A. Goldbeter and G. Nicolis, An allosteric enzyme model with positive feedback applied to glycolytic oscillations. In *Progress in Theoretical Biology* (F. Snell, R. Rosen, ed.), Vol. 4, pp. 65–160, Academic Press, New York (1976).
17. B. C. Goodwin, *Temporal Organization in Cells*, Academic Press, New York (1963).
18. R. Thom, *Stabilité Structurelle et Morphogenèse*, W. A. Benjamin, New York (1972).
19. J. Monod, J. Wyman, and J. P. Changeux, On the nature of allosteric transition: a plausible model. *J. Mol. Biol.* **12**, 88–118 (1965).
20. G. Yagil, Enzyme induction. In *Mathematical Models in Molecular and Cellular Biology* (L. A. Segel, ed.), pp. 68–83, Cambridge University Press, Cambridge (1980).
21. J. I. Rubinow and L. A. Segel, Positive and negative cooperativity. In *Mathematical Models in Molecular and Cellular Biology* (L. A. Segel, ed.), pp. 39–54, Cambridge University Press, Cambridge (1980).
22. H. Meinhardt, Models for the ontogenetic development of higher organisms. *Rev. Physiol. Biochem. Pharmacol.* **80**, 69–91 (1978).
23. F. J. Varela, *Principles of Biological Autonomy*, North-Holland, New York (1979).
24. S. Braten, Systems research and social science. In *Applied General Systems Research* (G. Klir, ed.), pp. 655–685, Plenum Press, New York (1978).
25. B. Rybak, Logique des systèmes vivants. In *Encyclopedia Universalis*, Paris (1968).
26. G. Bateson, *Steps to an Ecology of Mind*, Ballantine, New York (1972).
27. P. Delattre, Direct and inverse regulation control in transformation systems. *Math. Biosci.* **34**, 303–324 (1977).
28. E. Bernard-Weil, *L'Arc et la Corde*, Maloine, Paris (1975).
29. E. Bernard-Weil, Théologie et systémique, in *Violence et Vérité* (P. Dumouchel, ed.), pp. 93–109, Grasset, Paris (1985).
30. E. Bernard-Weil and B. Pertuiset, Mathematical model for hormonal therapy (corticoids, vasopressin) in cerebral collapse and malignant tumours of the brain (36 cases). *Neurol. Res.* **5**, 19–35 (1983).
31. E. Bernard-Weil and C. Da Lage, Inhibition by cortisol of the favourable effects of lysine-vasopressin on the growth of HeLa cell cultures. *Experientia* **24**, 1001 (1968).
32. E. Rozengurt, A. Legg, and P. Pettican, Vasopressin stimulation of mouse 3T3 cell growth. *Proc. Natl. Acad. Sci.* (USA) **76**, 1284–1287 (1973).
33. M. E. Monaco, P. H. Kohn, W. R. Kidwell, J. S. Strobl, and M. E. Lippman, Vasopressin action on WRK-1 rat mammary tumor cells. *JNCI* **68**, 267–270 (1982).
34. E. Bernard-Weil, Gilbert-Dreyfus, M. David, M. Sachs and J. Sebaoun, Evaluation of an antidiuretic effect in cancer. *Lancet* **II**, 324–326 (1967).
35. D. T. Krieger, W. Allen, F. Rizzo, and H. P. Krieger, Characterization of the normal temporal pattern of plasma corticosteroid levels. *J. Clin. Endocrin. Metab.* **32**, 266–284 (1971).
36. C. P. L. George, F. H. Messerli, J. Genest *et al.*, Diurnal variations of plasmatic vasopressin in man. *J. Clin. Endocrin. Metab.* **41**, 332–338 (1975).